DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

OCT 28 1997

TRANSMITTED VIA FACSIMILE

Elizabeth M. Rutherford
Counsel
Legal Division
Procter & Gamble Pharmaceuticals, Inc.
Blue Ash Office Center
Cincinnati, Ohio 45242-4716

RE: NDA # 20-064
Macrobid (nitrofurantoin monohydrate/macrocrystals)
MACMIS ID # 5752

Dear Ms. Rutherford:

Reference is made to Procter & Gamble Pharmaceuticals' (P&G) May 21, 1997, July 3, 1997, and July 10, 1997, submissions of promotional materials under cover of FDA Form 2253 for Macrobid (nitrofurantoin monohydrate/macrocrystals). These submissions include journal ad # MA967-140, brochure #MA967-49/PBM/SA and brochure # MA967-12. The Division of Drug Marketing, Advertising and Communications (DDMAC) has reviewed these promotional materials and finds them to be misleading in violation of the Federal, Food, Drug and Cosmetic Act and the applicable regulations.

Presentation of Safety Information

Brochure # MA967-49/PBM/SA is misleading because it fails to include adequate risk information associated with the use of Macrobid. Promotional materials must present information relating to contraindications, warnings, precautions, and adverse effects with a prominence and readability reasonably comparable with the presentation of information relating to effectiveness. The above brochure contains effectiveness claims but fails to include an adequate presentation of risk information associated with the use of Macrobid. For example, this promotional piece fails to include the information regarding the bolded warning or that the most common side effects associated with the use of Macrobid are nausea (8%), headache (6%), and flatulence (5.5%). Furthermore, the brochure fails to disclose that Macrobid is contraindicated in patients with a creatinine clearance <60ml per minute.

Compliance Claims

"Your Chances of COMPLIANCE may be Improved With B.I.D. Dosing"

The presentation following this sub-header appearing in brochure # MA967-49/PBM/SA, including the above statement and accompanying graphic matter, is misleading. Specifically, the graphic presentation states or suggests that better compliance rates were demonstrated with a twice daily dosing (b.i.d.) regimen versus a four-times-daily (q.i.d.) dosing regimen, i.e., 70% and 42% respectively. Since this graphic presentation appears as part of a brochure to promote Macrobid for the treatment of acute cystitis, it suggests that the data relied upon to support the compliance rate claim describes patients with acute cystitis that used Macrobid. Thus, the promotional materials suggest that compliance would improve in patients with acute cystitis if Macrobid were used twice daily instead of other medications used four times a day.

Additionally, the reference cited in support of the compliance claim, Greenburg, RN,[1] is a retrospective analysis of data from various articles and book chapters that discuss patient compliance, generally, and is based on the dosing of a variety of medications for a variety of uses. The referenced study did not discuss Macrobid or the use of Macrobid by patients with acute cystitis. Therefore, this study does not support a specific patient compliance claim for the use of Macrobid.

Although P&G provides a disclaimer stating that "Macrobid was not included in this study," such disclaimers cannot correct untrue or misleading information.

Cost Presentation

The graphic presentation of cost claims in brochure # 967-49/PBM/SA and the accompanying statement "Macrobid costs up to 58% less per day than the following leading fluoroquinolones and less than Macrodantin" are misleading. P&G suggests that Macrobid is as effective as fluoroquinolones in treating acute cystitis and costs less. However, the graphic presentation fails to reveal material facts concerning the efficacy rates and costs of other medications that may be comparable or superior to Macrobid in treating acute cystitis, but costs less.

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[1] Greenburg, RN, Overview of Patient Compliance with Medication Dosing: A Literature Review. Clin Ther. 1984; 16:592-599.

Specifically, P&G compares Macrobid to products such as ampicillin and TMP/SMX when it makes effectiveness claims and compares it to Macrodantin, Floxin, Cipro, and Noroxin, when it makes cost claims.

We note that the statement:

> Lower acquisition cost alone does not necessarily reflect a cost advantage. In the absence of comparative efficacy data, products that are the subject of this price comparison are not known to have comparable efficacy.

appears as a footnote to the comparative cost presentation. Nonetheless, the claims are misleading because they fail to reveal material facts concerning the effectiveness and costs of the products compared in the presentation.

Efficacy Claims

Journal ad # MA967-140 is misleading because it contains a misleading effectiveness claim. Specifically, the claim "The uncomplicated cure," is misleading because it lacks material facts and fails to present efficacy data to provide context for the claim. Specifically, the journal ad fails to state the medical condition and causative pathogens that Macrobid is indicated to treat and limitations, because of the lower eradication rates, obtained with Macrobid. The journal ad also fails to include the efficacy rate demonstrated in clinical studies used as the basis of approval. In these clinical studies, Macrobid demonstrated a 75% microbiologic eradication of susceptible pathogens. Thus, failure to include the indication, causative pathogens, limitations, and supporting clinical data makes this presentation misleading.

Brochure # 967-12 is misleading because it contains misleading effectiveness claims. Specifically, the claim "In clinical trials, Macrobid achieved 93% clinical success (71% cured + 22% improved) is misleading because it lacks material facts and fails to present the efficacy rate demonstrated in clinical studies used as the basis of approval. As stated above, Macrobid demonstrated a 75% microbiologic eradication of susceptible pathogens. Additionally, UTI is a condition that is easy to evaluate. Patients are either cured or not cured after treatment for this infection. Clinical success is based on bacteriologic eradication and resolution of the constellation of symptoms associated with a UTI (e.g. dysuria, urinary frequency, urgency, etc). Cure + improvement are not applicable to evaluating a UTI. To the

contrary, the labeling for Macrobid calls for culture and susceptibility testing after completion of therapy and if persistence or reappearance of bacteriuria occurs after treatment with Macrobid, other therapeutic agents with broader tissue distribution should be selected. Thus, failure to include this important information makes the clinical effectiveness claims misleading.

Comparison of *In-Vitro* Data

Brochure # 927-12 is misleading because it contains a presentation of MIC data that implies that Macrobid has greater efficacy or is superior to other products in treating acute cystitis due to *E coli* or *S saprophyticus*, when such effectiveness has not been demonstrated by an adequate and well-controlled, head-to-head clinical study. Specifically, the presentation states the *in vitro* susceptibility rates for nitrofurantoin, ampicillin, and trimethoprim/sulfamethoxazole for *E. coli* as 98%, 67%, and 87%, respectively and for *S. saprophyticus* as 98%, 74%, and 86%, respectively. According to P&G, the above stated susceptibility rates were derived from an Antibacterial Surveillance Study-1994. This presentation is misleading because it suggests that Macrobid is clinically superior to ampicillin and trimethoprim/sulfamethoxazole without substantial evidence for support.

Although P&G provides a disclaimer that states that "The following *in vitro* data are available, however, their clinical significance is unknown," this disclaimer cannot correct the misleading claim that Macrobid is superior to ampicillin and trimethoprim/sulfamethoxazole in treating acute cystitis caused by *E. coli* or *S. saprophyticus*.

In order to address these objections, DDMAC recommends that P&G take the following actions:

1. Immediately discontinue the use of all brochures and journal ads and any other promotional materials for Macrobid that contain the same or similar violations.

2. Provide a written response to DDMAC of your intent to comply with the above request and a list of promotional materials, containing the misleading presentations, that will be discontinued.

P&G's response should be received no later than November 11, 1997. If P&G has any questions or comments, please contact the undersigned by facsimile at (301)

594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-40, Rm 17B-20, 5600 Fishers Lane, Rockville, MD 20857.

In all future correspondence regarding this particular matter, please refer to MACMIS ID # 5752 in addition to the NDA number.

Sincerely,

Jo Ann Spearmon, Pharm.D., M.P.A.
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications